Corneal Aberrations in Former Preterm Infants: Results From The Wiesbaden Prematurity Study

Achim Fieß,[1,2] Alexander K. Schuster,[2] Ruth Kölb-Keerl,[1] Markus Knuf,[3] Bernd Kirchhof,[4] Philipp S. Muether,[4] and Jacqueline Bauer[3]; for the Prematurity Eye Study Group

[1]Department of Ophthalmology, Helios Dr. Horst Schmidt Klinik Wiesbaden, Germany
[2]Department of Ophthalmology, University Medical Center Mainz, Mainz, Germany
[3]Department of Pediatrics, Helios Dr. Horst Schmidt Klinik Wiesbaden, Germany
[4]Department of Ophthalmology, University of Cologne, Germany

PURPOSE. To compare corneal aberrations in former preterm infants to that of full-term infants.

METHODS. A prospective cross-sectional study was carried out measuring the corneal shape with Scheimpflug imaging in former preterm infants of gestational age (GA) ≤ 32 weeks and full-term infants with GA ≥ 37 weeks now being aged between 4 to 10 years. The main outcome measures were corneal aberrations including astigmatism (Zernike: Z^2_{-2}; Z^2_2), coma (Z^3_{-1}; Z^3_1), trefoil (Z^3_{-3}; Z^3_3), spherical aberration (Z^4_0) and root-mean square of higher-order aberrations (RMS HOA). Multivariable analysis was performed to assess independent associations of gestational age groups and of retinopathy of prematurity (ROP) occurrence with corneal aberrations adjusting for sex and age at examination.

RESULTS. A total of 259 former full-term and 226 preterm infants with a mean age of 7.2 ± 2.0 years were included in this study. Statistical analysis revealed an association of extreme prematurity (GA ≤ 28 weeks) with higher-order and lower-order aberrations of the total cornea. Vertical coma was higher in extreme prematurity ($P < 0.001$), due to the shape of the anterior corneal surface, while there was no association with trefoil and spherical aberration. ROP was not associated with higher-order aberrations when adjusted for gestational age group.

CONCLUSIONS. This study demonstrated that specific corneal aberrations were associated with extreme prematurity rather than with ROP occurrence.

Keywords: retinopathy of prematurity, low gestational age, low birth weight, cornea, corneal aberrations

The effects of prematurity and postnatal occurrence of retinopathy of prematurity (ROP) on altered ocular organ development in infancy are well known, especially its effect on the anterior eye segment. Former preterm infants have an increased risk for steeper corneal curvature,[1–3] shallower anterior chamber,[4] thicker lens,[4,5] and smaller axial length.[3,5] In addition, these infants present higher refractive errors.[6]

New imaging modalities using Scheimpflug principles allow contactless and detailed measurements of corneal and anterior segment morphology with high reproducibility and repeatability.[7,8] Additionally, this technology enables the measurement of corneal aberrations and mathematically distinguishes the different properties as described by Zernike (Z) coefficients. To date, there has only been one study reporting corneal aberrations in former preterm infants with Scheimpflug imaging,[5] showing increased corneal higher-order aberrations in former preterm infants in this population at age 7 to 14 years. It is still under discussion whether corneal higher-order aberrations contribute, as one of various factors, to the increased risk of former preterm infants for deteriorated visual acuity compared to full-term infants.

Hence, the focus of this investigation was to compare corneal aberrations of former preterm infants and former full-term neonates, and to evaluate differences in the various corneal aberrations in relation to gestational age and retinopathy of prematurity occurrence.

METHODS

This study was conducted in accordance with the tenets of the Declaration of Helsinki. Study approval was obtained from the local ethics committee (Physician Chamber Hessen). Written informed consent was obtained from the parents or legal guardian of each child. The authors declare no financial or proprietary conflict of interest.

The present study analyzed infants examined within the Wiesbaden Prematurity Study (WPS) in the Dr. Horst Schmidt Klinik Wiesbaden in Germany from July 2014 to March 2015. For the WPS, all premature infants born in our hospital with a gestational age (GA) below 33 weeks and actual age between 4 to 10 years were contacted and invited for detailed ophthalmologic examination. Randomly selected full-term infants with a GA ≥ 37 weeks served as the control group. The exclusion criteria of the WPS were the presence of severe congenital anomalies since birth. Severe congenital anomalies were defined as infants with congenital chromosomal disorders or/and congenital heart diseases, or/and neural tube defects.

WPS participants were included in this analysis if measurement of corneal parameters by Scheimpflug imaging was possible without significant movement or artefacts. In addition, the scan quality had to be sufficient for the automated assessment of corneal aberrations. Children were excluded from the analysis if corneal tomography was not possible and if the scan quality was too low due to unstable fixation or low compliance as reported earlier.[3]

Corneal tomography and imaging were performed in all study participants using a Pentacam HR rotating Scheimpflug camera as reported earlier.[3] In brief, Pentacam imaging allows three-dimensional imaging of the anterior segment from the anterior corneal surface to the posterior lens surface. All measurements were standardized according to the instruction manual by an examiner masked for the study purpose. When fulfilling the requirements for optimal alignment, corneal tomography was measured within 2 seconds based on 25 Scheimpflug images. To assure high quality for all investigations, the quality description of the device was checked and only accepted if "OK" was displayed. In the case that "OK" was not displayed or if comments colored yellow or red appeared, further measurements were conducted. The following corneal aberration parameters were documented for the present analysis: oblique and vertical astigmatism (Z^2_{-2}; Z^2_2); vertical and horizontal coma (Z^3_{-1}; Z^3_1); vertical and oblique trefoil (Z^3_{-3}; Z^3_3); spherical aberration (Z^4_0); and root-mean square of higher-order aberrations (RMS HOA) and of lower-order aberrations (LOA). All parameters were assessed for total cornea, for corneal front surface and for corneal back surface. Zernike parameters were calculated on an optic zone of 6 mm diameter and with a refractive index of 1.3375.

Medical records were used to assess the peri- and postnatal history of each study participant. All parents of WPS infants completed a detailed questionnaire. Only data of the right eye were included in the statistical analysis.[9]

Statistical Analyses

For descriptive analysis, infants were grouped into full-term infants with GA ≥ 37 weeks (group 1); preterm infants of GA between 29 and 32 weeks without ROP (group 2); preterm infants of GA ≤ 28 weeks without ROP (group 3); and preterm infants with GA ≤ 32 weeks and presence of ROP (group 4).[3]

Continuous variables were expressed as means $\pm$ SD or as median values when appropriate. Categorical variables were expressed as proportions. A χ^2 test was used to analyze differences between groups for categoric variables. The normal distribution of data was tested using the Kolmogorov-Smirnov test. The Kruskal-Wallis test was used to compare independent continuous parameters between several groups. Corneal aberration values were compared in a multivariable linear regression model per corneal aberration type, including this as a depending variable and gestational age in the groups (full term infants [GA ≥ 37 weeks]; GA 29–32 weeks; GA ≤ 28 weeks); and ROP occurrence (yes/no) as independent variables, adjusted for sex and age at examination. This enabled the effect of gestation age and ROP to be reported independently from each other. The nonstandardized coefficient B and 95% confidence interval (CI) were calculated. As this is an explorative study, P values should be regarded as a continuous parameter reflecting the level of evidence; therefore, they are reported exactly. Furthermore, to adjust for multiple testing according to Bonferroni's correction, a P value ≤ 0.0025 (having performed 20 tests for analysis of total corneal aberrations) was considered as statistically significant. Calculations were performed using commercial software (IBM SPSS 20.0; SPSS, Inc., Chicago, IL, USA).

RESULTS

Participants' Characteristics

Overall, successful Pentacam imaging was recorded for 485 of 503 children. Of these, 259 of 264 were born full term (group 1); 124 of 125 were born with a GA between 29 and 32 weeks without ROP (group 2); 51 of 59 were born with GA ≤ 28 weeks without ROP (group 3); and 51 of 55 were formerly preterm infants with postnatal ROP occurrence (group 4). Overall, 28 infants of group 4 had postnatal occurrence of stage one ROP, 13 had postnatal occurrence of stage 2 ROP and 10 infants had postnatal occurrence of stage 3 ROP. Only 13 infants of group 4 with ROP had a gestational age ≥ 29 weeks (range between 29 and 30 weeks), 11 of them had a history of ROP stage 1 and two infants with ROP stage 2. Diode laser treatment was performed in six infants. The following ophthalmic variables, visual acuity, spherical equivalent, and astigmatism were reported earlier for this cohort.[3] In groups 1 to 4, 123/259 (47.5%); 71/124 (57.3%); 26/51 (51%); and 26/51 (51%) of children were male ($P = 0.37$) and mean age was 7.2 $\pm$ 2.0 in group 1; 7.0 $\pm$ 1.8 in group 2; 6.9 $\pm$ 2.1 in group 3; 7.6 $\pm$ 2.2 in group 4, ($P = 0.18$), respectively.

Corneal Aberrations

Descriptively, total corneal aberrations, lower-order aberrations and higher-order aberrations increased when GA was lower (Table 1). This was mainly seen on the corneal front surface (Supplementary Tables S1, S2). All total corneal aberrations are described in Table 1 and for gestational age groups without ROP occurrence in the Figure.

In multivariable analysis, extreme prematurity (GA ≤ 28 weeks) was associated with higher vertical coma (Z^3_{-1}), and higher total aberrations and increased higher-order and lower-order aberrations (Table 2), which was mainly due to the corneal front surface. Associations with aberrations of corneal front and corneal back surface are described in Supplementary Table S1 and S2.

Retinopathy of prematurity was not associated with higher-order or lower-order aberrations of the total cornea when data was adjusted for gestational age groups.

DISCUSSION

This study analyzed corneal aberrations with Scheimpflug imaging in former preterm and full-term infants, evaluating the impact of gestational age and the occurrence of ROP on corneal aberrations. Our report highlights that especially extreme prematurity (GA ≤ 28 weeks) was associated with vertical coma, total higher-order and lower-order aberrations of the total cornea, demonstrating that specific corneal aberrations were associated with extreme prematurity. These alterations of corneal aberrations in prematurity were mainly due to the shape of the anterior corneal surface, while the posterior corneal surface did not show these dependencies. Retinopathy of prematurity showed no impact on higher-order aberrations of total cornea when adjusted for gestational age, indicating that prematurity rather than ROP leads to higher order aberrations of the corneal shape.

Premature delivery abruptly leads to fetal environmental changes associated with altered ocular and corneal development including steeper corneal curvature.[1–3] In an previous report, Fiedler et al.[10] hypothesized that lower extrauterine temperature after early delivery may be a factor contributing to a less flattening of the cornea. No difference in corneal thickness was observed between former preterm and full-term participants at the age of 7 and 14 years assessed with

TABLE 1. Total Corneal Aberrations Stratified for GA and ROP*

	Group 1, ≥37 wk, n = 259	Group 2, 29–32 wk, no ROP, n = 124	Group 3, ≤28 wk, no ROP, n = 51	Group 4, ≤32 wk, With ROP, n = 51	P Value*
Astigmatism					
Oblique (Z^2_{-2})	−0.106 ± 0.385	0.004 ± 0.440	0.011 ± 0.334	−0.018 ± 0.487	0.09
Vertical (Z^2_2)	−0.600 ± 0.456	−0.617 ± 0.612	−0.745 ± 0.603	−0.513 ± 0.761	0.25
Coma					
Horizontal (Z^3_1)	−0.066 ± 0.174	−0.063 ± 0.208	−0.072 ± 0.219	−0.098 ± 0.280	0.92
Vertical (Z^3_{-1})	−0.032 ± 0.178	−0.003 ± 0.180	0.098 ± 0.197	0.037 ± 0.163	<0.001
Trefoil					
Oblique (Z^3_3)	−0.012 ± 0.163	0.009 ± 0.144	−0.005 ± 0.129	−0.031 ± 0.237	0.55
Vertical (Z^3_{-3})	−0.063 ± 0.146	−0.052 ± 0.183	−0.123 ± 0.202	−0.061 ± 0.231	0.29
Spherical aberration (Z^4_0)	0.151 ± 0.072	0.156 ± 0.079	0.152 ± 0.102	0.142 ± 0.104	0.83
Corneal aberrations (RMS)					
Total	1.264 ± 0.443	1.392 ± 0.590	1.488 ± 0.541	1.543 ± 0.680	0.001
HOA	0.404 ± 0.174	0.429 ± 0.176	0.473 ± 0.218	0.517 ± 0.273	0.002
LOA	1.188 ± 0.433	1.319 ± 0.578	1.399 ± 0.525	1.434 ± 0.670	0.002

All aberrations are reported in μm. Only data of the right eye were included in the analysis, and the Kruskal-Wallis test was used to compare data between the different groups. *n*, number of children.

* Group 1 (full-term born infants with a GA ≥37 weeks); group 2 (preterm infants with a GA between 29 and 32 weeks without ROP); group 3 (preterm infants with a GA ≤28 weeks without ROP); group 4 (preterm infants with GA ≤32 weeks with ROP).

Scheimpflug imaging.[5] With respect to corneal shape, Ecsedy et al.[5] reported that preterm infants with and without ROP have a higher measures of corneal higher-order aberrations. However, this investigation reports on small and heterogeneous study groups including preterm infants with and without ROP in one study group. In contrast, our study provides data about the less studied influence of prematurity (indicated with different GA groups), and additional data about the potential influence of postnatal ROP occurrence after birth on corneal aberrations in the age of 4 to 10 years. Using our statistical model, we could separate the effect of GA and ROP, demonstrating that lower GA ≤28 weeks is a factor leading to increased corneal higher- and lower-order aberrations in contrast to ROP, which does not appear to influence corneal aberrations independently from gestational age.

The development of corneal shape and the eye globe is regulated by several factors, with some authors supporting that genetic factors determine corneal topography. Valluri et al.[11] found that there is a genetic predisposition for axial length and spherical equivalent of refractive error when analyzing twins. However, for corneal topography the authors concluded that other nongenetic factors seem to be more important. Hammond et al.[12] reported that nearly half of the variance of astigmatism can be explained by genetic reasons. Furthermore, Tabernero et al.[13] investigated whether corneal aberrations are genetically or environmentally determined by analyzing 138 eyes of 69 twins. They confirmed that genes play an important role in the variance of corneal aberrations. For instance, the heritability of corneal spherical aberration was reported to be 52%,[13] while a prior Korean population-based study identified 20%.[14]

Intraocular pressure is considered as another factor affecting the development of the eye. Looking on the extremes, infants with childhood glaucoma develop long axial length, have large corneal diameter and flatter corneal curvature. Corneal astigmatism is increased in the 5 mm zone in these children and is also configured more irregularly.[15] Furthermore, Yang et al.[16] observed in a school based study of 1911 children that higher intraocular pressure correlated with steeper corneal curvature and younger age. The curvature of the cornea is also thought to be linked with birthweight.[17] Similarly, a twin study investigating 1498 participants aged between 5 to 80 years found that low birthweight was associated with a more curved cornea.[18] It is possible that these associations may also contribute to alterations in corneal aberrations in former preterm infants.

Yinon et al.[19] observed in an animal study that suturing the eyelids of kittens during eye development leads to an increase of astigmatism, both in the sutured eye and in the fellow eye, while the controls had less astigmatism. This data indicates that lid movements affect the development of astigmatism potentially affecting the development of corneal aberrations. Astigmatism is thought to be mainly due to corneal astigmatism in younger age and in with-the-rule position.[20] Differences in the palpebral position might have an effect on corneal astigmatism. Indeed, Grey et al.[21] found that narrowing the palpebral aperture leads to increased cylindrical error, while Read et al.[22] reported that corneal cylinder axis correlates with the eyelid angle. Nevertheless, Raffa et al.[23] did not find an association of palpebral fissure length with gestational age or birthweight.
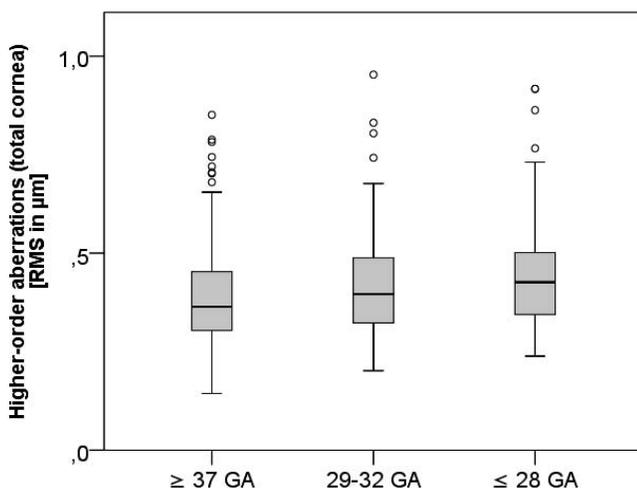

FIGURE. *Boxplots* presenting higher-order aberrations of the total cornea for each group without postnatal ROP occurrence: group 1 (full-term born infants with a GA ≥37 weeks); group 2 (preterm infants with a GA between 29 and 32 weeks without ROP); and group 3 (preterm infants with a GA ≤28 weeks without ROP).

TABLE 2. Linear Regression Model Analyzing the Association of Total Corneal Aberrations of the Different GA Groups and ROP Adjusted for Age at Examination and Sex

Linear Regression Model N = 485	GA ≥37 wks Ref.	GA 29–32 wks		GA ≤28 wks		ROP (yes)	
		B (95% CI)	*P* Value	B (95% CI)	*P* Value	B (95% CI)	*P* Value
Astigmatism							
Oblique (Z^2_{-2})	Ref.	0.11 (0.02; 0.19)	0.013	0.11 (−0.01; 0.23)	0.06	−0.02 (−0.16; 0.12)	0.77
Vertical (Z^2_2)	Ref.	−0.02 (−0.14; 0.10)	0.74	−0.15 (−0.30; 0.01)	0.07	0.20 (0.01; 0.39)	0.038
Coma							
Horizontal (Z^3_1)	Ref.	0.01 (−0.04; 0.05)	0.79	−0.01 (−0.07; 0.05)	0.68	−0.03 (−0.09; 0.04)	0.46
Vertical (Z^3_{-1})	Ref.	0.03 (−0.01; 0.07)	0.07	0.12 (0.07; 0.17)	<0.001	−0.04 (−0.10; 0.03)	0.24
Trefoil							
Oblique (Z^3_3)	Ref.	0.03 (−0.01; 0.06)	0.14	0.001 (−0.05; 0.05)	0.97	−0.03 (−0.08; 0.03)	0.36
Vertical (Z^3_{-3})	Ref.	0.01 (−0.03; 0.05)	0.61	−0.04 (−0.09; 0.01)	0.07	0.03 (−0.02; 0.09)	0.25
Spherical aberration (Z^4_0)	Ref.	0.01 (−0.01; 0.03)	0.29	−0.002 (−0.02; 0.02)	0.87	−0.01 (−0.04; 0.01)	0.35
Corneal aberrations (RMS)							
Total	Ref.	0.10 (−0.01; 0.21)	0.06	0.28 (0.13; 0.42)	<0.001	0.06 (−0.12; 0.24)	0.5
HOA	Ref.	0.02 (−0.02; 0.06)	0.43	0.09 (0.03; 0.14)	0.002	0.05 (−0.01; 0.12)	0.11
LOA	Ref.	0.11 (0.001; 0.22)	0.048	0.26 (0.12; 0.40)	<0.001	0.04 (−0.14; 0.21)	0.68

Corneal aberration values were compared in a multivariable linear regression model per corneal aberration type, including this as a depending variable and GA in the groups (full-term infants [GA ≥ 37 weeks]; GA 29–32 weeks; GA ≤ 28 weeks) and ROP occurrence (yes/no) as independent variables, adjusted for sex and age at examination. The nonstandardized coefficient B and 95% CI were calculated. Only data of the right eye were included in the analysis. Ref., reference.

Overall, prematurity leads to altered ocular growth and morphologic alterations like a steeper cornea,[3,4] smaller anterior chamber depth,[4] thicker lens,[4] and smaller axial length[3] in childhood, which contributes to refractive error development and probably to altered corneal HOA and LOA.

To date, it is unclear whether these associations and/or environmental changes after preterm delivery may affect corneal aberrations. However, it is well known that preterm birth completely changes the newborns' environment; therefore, it is likely that different factors associated with prematurity contribute to the altered corneal aberrations in preterm infants. Optical aberrations lead to visual disturbance, degraded retinal image quality, and play a role in the emmetropization processes potentially influencing refractive error development.[24] Prematurity and ROP are well-known risk factors for myopic refractive error,[25] which is also applicable in our study sample.[3] In previous reports, some authors hypothesized that peripheral corneal aberrations have an impact on development and progression of myopia.[26] In accordance, an association between myopia and corneal aberrations was observed.[27] Supporting this hypothesis, Paquin et al.[28] reported higher amounts of coma aberrations in highly myopic eyes. Furthermore, increased corneal aberrations may be one of several factors contributing to low visual function particularly in extremely preterm infants. However, the visual effects of ocular aberrations are small compared to myopia and astigmatism[29] and in addition, image optical quality is only one of several factors of visual perception but may play a role in deteriorated visual perception in preterm infants.

Study Limitations

The strengths of our study are the large sample size with preterm infants with and without ROP as well as the large control group. Limitations are the single center study design and that some parents declined to participate in the study. Although Scheimpflug examination was quality controlled, poorer fixation control in the extremely preterm infants may have had an influence on corneal aberration measurements particularly in extreme preterm infants. In addition, we were not able to evaluate the impact of corneal aberrations on the optical quality of the eye in prematurity as ocular wavefront measurements were not performed.

Conclusions

In conclusion, this study has for the first time revealed an association of extreme prematurity (GA ≤28) with higher-order and lower-order aberrations as well as with higher vertical coma, independently of ROP status. In contrast, ROP was not associated with total higher-order aberrations of the total cornea when the data was adjusted for gestational age. These results demonstrated that specific corneal aberrations were associated with extreme prematurity potentially contributing as another factor to myopic refractive error, and visual dysfunction in extreme preterm infants.

References

1. Kirwan C, O'Keefe M, Fitzsimon S. Central corneal thickness and corneal diameter in premature infants. *Acta Ophthalmol Scand*. 2005;83:751–753.

2. Saw SM, Tong L, Chia KS, et al. The relation between birth size and the results of refractive error and biometry measurements in children. *Br J Ophthalmol*. 2004;88:538–542.

3. Fieß A, Kolb-Keerl R, Knuf M, Hocaoglu M, Arf S, Ozdemir H. Axial length and anterior segment alterations in former preterm infants and full-term neonates analyzed with Scheimpflug imaging. *Cornea*. 2017;36:821–827.

4. Wu WC, Lin RI, Shih CP, et al. Visual acuity, optical components, and macular abnormalities in patients with a history of retinopathy of prematurity. *Ophthalmology*. 2012; 119:1907–1916.

5. Ecsedy M, Kovacs I, Mihaltz K, et al. Scheimpflug imaging for long-term evaluation of optical components in Hungarian

children with a history of preterm birth. *J Pediatr Ophthalmol Strabismus*. 2014;51:235–241.

6. Hwang CK, Hubbard GB, Hutchinson AK, Lambert SR. Outcomes after intravitreal bevacizumab versus laser photocoagulation for retinopathy of prematurity: a 5-year retrospective analysis. *Ophthalmology*. 2015;122:1008–1015.

7. Ho T, Cheng AC, Rao SK, Lau S, Leung CK, Lam DS. Central corneal thickness measurements using Orbscan II, Visante, ultrasound, and Pentacam pachymetry after laser in situ keratomileusis for myopia. *J Cataract Refract Surg*. 2007;33:1177–1182.

8. Chen D, Lam AK. Intrasession and intersession repeatability of the Pentacam system on posterior corneal assessment in the normal human eye. *J Cataract Refract Surg*. 2007;33:448–454.

9. Fan Q, Teo YY, Saw SM. Application of advanced statistics in ophthalmology. *Invest Ophthalmol Vis Sci*. 2011;52:6059–6065.

10. Fielder AR, Levene MI, Russell-Eggitt IM, Weale RA. Temperature—a factor in ocular development? *Dev Med Child Neurol*. 1986;28:279–284.

11. Valluri S, Minkovitz JB, Budak K, et al. Comparative corneal topography and refractive variables in monozygotic and dizygotic twins. *Am J Ophthalmol*. 1999;127:158–163.

12. Hammond CJ, Snieder H, Gilbert CE, Spector TD. Genes and environment in refractive error: the Twin Eye Study. *Invest Ophthalmol Vis Sci*. 2001;42:1232–1236.

13. Tabernero J, Hervella L, Benito A, et al. Micrometric control of the optics of the human eye: environment or genes? *Invest Ophthalmol Vis Sci*. 2017;58:1964–1970.

14. Lim DH, Kim W, Han G, et al. The heritability of corneal and ocular higher-order aberrations in Koreans: the Healthy Twin Study. *Invest Ophthalmol Vis Sci*. 2015;56:3919–3928.

15. Patil B, Tandon R, Sharma N, et al. Corneal changes in childhood glaucoma. *Ophthalmology*. 2015;122:87–92.

16. Yang DY, Guo K, Wang Y, et al. Intraocular pressure and associations in children. The Gobi Desert Children Eye Study. *PLoS One*. 2014;9:e109355.

17. Fieß A, Schuster AK, Pfeiffer N, Nickels S. Association of birth weight with corneal power in early adolescence: results from the National Health and Nutrition Examination Survey (NHANES) 1999 – 2008. *PLoS One*. 2017;12:e0186723.

18. Sun C, Ponsonby AL, Brown SA, et al. Associations of birth weight with ocular biometry, refraction, and glaucomatous endophenotypes: the Australian Twins Eye Study. *Am J Ophthalmol*. 2010;150:909–916.

19. Yinon U, Koslowe KC, Rassin MI. The optical effects of eyelid closure on the eyes of kittens reared in light and dark. *Curr Eye Res*. 1984;3:431–439.

20. Sanfilippo PG, Yazar S, Kearns L, Sherwin JC, Hewitt AW, Mackey DA. Distribution of astigmatism as a function of age in an Australian population. *Acta Ophthalmol*. 2015;93:e377–e385.

21. Grey C, Yap M. Influence of lid position on astigmatism. *Am J Optom Physiol Opt*. 1986;63:966–969.

22. Read SA, Collins MJ, Carney LG. The influence of eyelid morphology on normal corneal shape. *Invest Ophthalmol Vis Sci*. 2007;48:112–119.

23. Raffa LH, Hellstrom A, Aring E, Andersson S, Gronlund MA. Ocular dimensions in relation to auxological data in a sample of Swedish children aged 4-15 years. *Acta Ophthalmol*. 2014;92:682–688.

24. Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. *Neuron*. 2004;43:447–468.

25. Larsson EK, Rydberg AC, Holmstrom GE. A population-based study of the refractive outcome in 10-year-old preterm and full-term children. *Arch Ophthalmol*. 2003;121:1430–1436.

26. Radhakrishnan H, Allen PM, Calver RI, et al. Peripheral refractive changes associated with myopia progression. *Invest Ophthalmol Vis Sci*. 2013;54:1573–1581.

27. Collins MJ, Wildsoet CF, Atchison DA. Monochromatic aberrations and myopia. *Vision Res*. 1995;35:1157–1163.

28. Paquin MP, Hamam H, Simonet P. Objective measurement of optical aberrations in myopic eyes. *Optom Vis Sci*. 2002;79:285–291.

29. Porter J, Guirao A, Cox IG, Williams DR. Monochromatic aberrations of the human eye in a large population. *J Opt Soc Am A Opt Image Sci Vis*. 2001;18:1793–1803.

APPENDIX

Participating investigators or collaborators who collected data or provided and cared for study patients (in alphabetical order): Luka Christian,[1] Serife Demirbas,[2] Paula Divis Di Oliveira,[2] Lisa Ernst,[1] Shirin Ghafoori,[2] Johannes Janz,[1] Saskia Jordan,[2] Petra Nikolic,[1] David Scheele,[1] Florian Tluczynski,[2] and Christine Zeymer.[1]

[1]Department of Pediatrics, Helios Dr. Horst Schmidt Klinik Wiesbaden, Germany
[2]Department of Ophthalmology, Helios Dr. Horst Schmidt Klinik Wiesbaden, Germany